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Spirocyclic Nonpeptide Glycoprotein IIb–IIIa Antagonists. Part 1: Design of Potent and Specific 3,9-Diazaspiro[5.5]undecanes

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Abstract—The synthesis and biological activity of novel glycoprotein IIb–IIIa antagonists containing the 3,9-diazaspiro[5.5]-undecane nucleus are described. The potent activity of these compounds as platelet aggregation inhibitors demonstrates the utility of the spirocyclic structures as a central template for nonpeptide RGD mimics.

The activation and aggregation of platelets is a critical component of arterial thrombosis and leads to a number of cardiovascular disease states including unstable angina, myocardial infarction, and arterial re-occlusion following coronary angioplasty procedures.[1,2] By preventing the final common pathway of platelet aggregation, fibrinogen receptor antagonists [also termed platelet glycoprotein (GP) IIb–IIIa antagonists] have been demonstrated to be more potent antiplatelet agents than other classes of drugs that inhibit specific platelet activation pathways such as aspirin, or the ADP receptor antagonists ticlopidine or clopidogrel.[3,4]

In the design of potent GPIIb–IIIa antagonists, the tripeptide sequence RGD has been utilized as the starting motif for generating many structurally diverse inhibitors.[4,5] A vast majority of the synthetic efforts have focused on developing novel templates onto which an acidic and a basic pharmacophore are appended which mimic the RGD sequence. Many of the reported antagonists contain constrained templates consisting of monocyclic and/or fused bicyclics ring structures.[4,6,7] Oral antagonists with some of these features have proceeded into large phase III clinical trials including xemilofiban, orbofiban, sibrafiban, and lotrafiban (Fig. 1). Although the discovery of structurally diverse templates leading to potent antagonists has been quite extensive, one type of constrained template that has received little attention contains spirocyclic ring systems. One example of a spirocyclic template in the GPIIb–IIIa antagonist field has been disclosed by the Dupont-Merck group.[8] Their efforts employing a spiro-isoxazolinylimide central template resulted in weakly

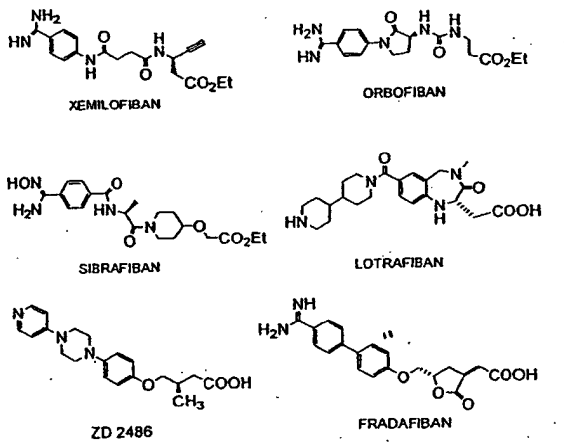

Figure 1. Representative oral nonpeptide GPIIb–IIIa antagonists in clinical development.

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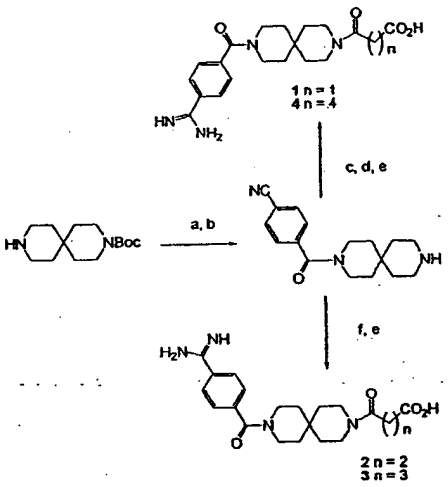
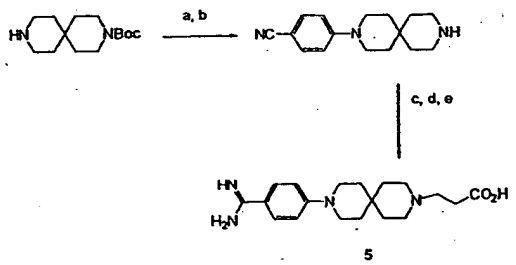
active compounds leading them to conclude that the steric bulk and/or rigidity of the spirocyclic template resulted in poor complimentarity with the receptor. There has been one additional report wherein the 3,9-diazaspiro[5.5]undecane ring system has been utilized as the basic pharmacophore unit, rather than as a central template to prepare GPIIb–IIIa antagonists.[9]

As part of our effort to discover novel antagonists with improved bioavailability and duration of action, we initially investigated the 3,9-diazaspiro[5.5]undecane ring system as a suitable template for preparing potent and selective GPIIb–IIIa antagonists. We initiated our investigation of spirocycles by choosing the 3,9-diazaspiro[5.5]undecane template, and also chose the benzamidine ring system as the basic group to append to this nucleus. However, we also wished to study less basic groups such as the 4-aminopyridyl residue found in the Zeneca inhibitor, ZD2496 (Fig. 1).[10] The lower pK_a of the pyridine moiety has been postulated to be a major reason for the excellent bioavailability reported for ZD2496.



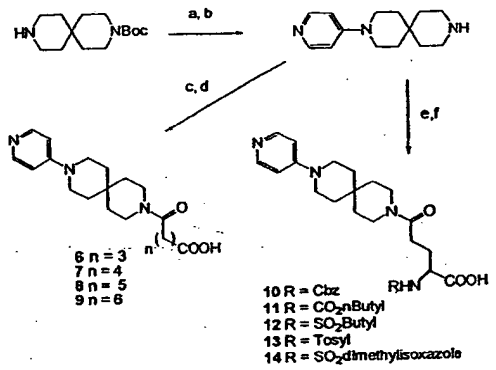
Scheme 1. Synthesis of compounds 1–4: (a) 4-cyanobenzoyl chloride, TEA, DCM, DMAP; (b) TFA/DCM; (c) $ClCO(CH_2)_{1,4}CO_2Et$, TEA, DCM; (d) 1 N NaOH; (e) (i) H_2S, Et_3N, Pyr; (ii) MeI, acetone, rt; (iii) NH_4OAc, EtOH, reflux; (f) succinic or glutaric anhydride, Et_3N, DCM.



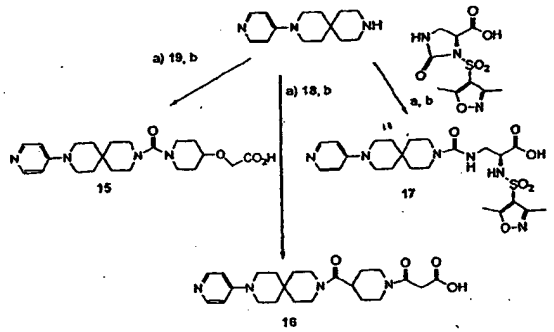
Scheme 2. Synthesis of compound 5: (a) 4-bromobenzonitrile, $Pd_2(dba)_3$·$CHCl_3$, S-BINAP, t-BuONa, toluene, 85 °C; (b) TFA/DCM; (c) $Br(CH_2)_2CO_2Et$, DIEA, DCM; (d) LiOH, THF, H_2O; (e) (i) NH_2OH·HCl, Et_3N, EtOH; (ii) Ac_2O, AcOH, rt; (iii) 1 atm H_2, 10% Pd/C, EtOH.

The synthesis of 3,9-diazaspiro[5.5]undecane nucleus follows published procedures.[9] A benzamidine moiety was incorporated using an amide or the direct linkage as shown in Schemes 1 and 2. The preparation of the required carboxylic acid side chains investigated in this study are shown in Schemes 5 and 6. Conversion of cyano to amidino functionality was carried out via the thiomethylimidate protocol or the hydroxyamidino method. The unsubstituted side-chain carboxylic acids used in compounds **1–4** (Scheme 1) and **6–9** (Scheme 3) were derived from the commercially available acid chloride esters or the appropriate anhydrides as shown in Schemes 1 and 3. Incorporation of the direct-linked benzamidines (Scheme 2) and 4-pyridyl groups (Scheme 3) into the spirocyclic template was accomplished utilizing a Pd-mediated coupling reaction.[11] Other more constrained carboxylic acid containing groups such as the piperidine-4-oxyacetic acid (Scheme 5 for synthesis) were coupled to the spiropyridine nucleus via the *p*-nitrophenylcarbamate intermediate as shown in Scheme 4.

The biological activity of the 3,9-diazaspiro[5.5]undecane-containing analogues prepared in this study were evaluated in vitro by measuring their ability to inhibit the binding of fibrinogen to purified human GPIIb–IIIa in a 96-well format.[12] The compounds were also evaluated in functional assays, which determined their



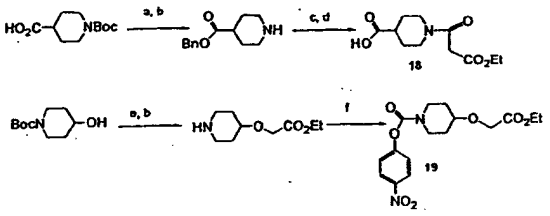
Scheme 3. Synthesis of compounds 6–9; (a) 4-bromopyridine, $Pd_2(dba)_3$·$CHCl_3$, S-BINAP, t-BuONa, toluene, 85 °C; (b) TFA/DCM; (c) $ClCO(CH_2)_{3-6}CO_2Et$, DIEA, DCM; (d) 2 M HCl; (e) 20–24, HOBt, DIEA, DMF; (f) 2 M HCl.



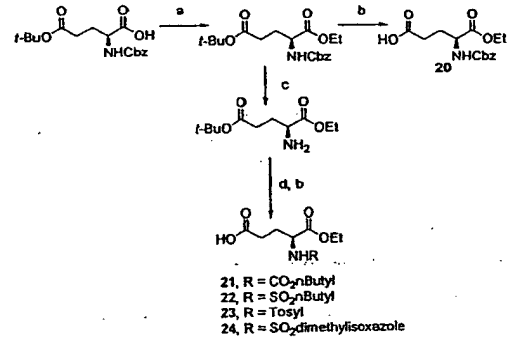
Scheme 4. Synthesis of compounds 15–17; (a) DMF, DIEA, 60 °C, DMF; (b) 2 M HCl.

ability to inhibit ADP-induced platelet aggregation in human platelet-rich plasma (PRP). Both benzamidine or pyridyl-containing analogues with simple carboxylic acid chains afforded modest potency (Tables 1 and 2). However, neither series displayed submicromolar IC_{50} values in PRP. From the initial series of pyridines, **6** appeared to have the optimal distance between the carbon atoms of the carboxylate and the basic nitrogen functionality, and this template was chosen for further structural modifications.

Incorporation of a rigid carboxylic acid moiety (analogues **15** and **16**, Table 3) did not provide additional potency enhancement in the plasma based assay relative to compound **6**. However, incorporation of α-amino substitution at the carboxylic acid segment significantly enhances the potency as seen for compounds **11–14** and **17** versus **6** (250-fold, Table 4). Incorporation of the 3,5-dimethylisoxazol-4-yl-sulfonamide moiety (**14** and **17**) stands out relative to other α-amino group substituents that were examined, affording inhibitors of ADP-induced aggregation in PRP with IC_{50} values <70 nM. These observations are consistent with the results published by Egbertson et al.[13] where it was proposed that the α-substituent of their tyrosine-derived GPIIb–IIIa antagonists may be interacting with an unexploited 'exosite' within GPIIb–IIIa leading to significant enhancement of the binding interactions. All active compounds of our spirocyclic series were found to have IC_{50} values >100 μM against the vitronectin receptor, $\alpha_v\beta_3$, the most closely related integrin to GPIIb–IIIa. Thus, both benzamidine and pyridine-containing analogues from

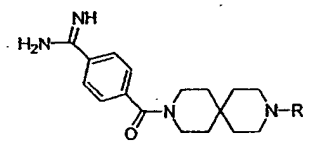


Scheme 5. Synthesis of carboxylic acid segments **18** and **19**. (a) BnOH, DCC, DMAP, DCM; (b) TFA, DCM; (c) $ClCOCH_2CO_2Et$, DIEA, DCM; (d) 10% Pd/C, H_2; (e) ethyl diazoacetate, $Rh(OAc)_2$-dimer; (f) *p*-nitrophenylchloroformate, DIEA, DMF.



Scheme 6. Synthesis of carboxylic acid segments **20–24**. (a) EDC, HOBt, EtOH; (b) TFA, DCM; (c) $Pd(OH)_2$, 1 atm H_2, EtOH; (d) RSO_2Cl or ROCOCl, DIEA, DMF.

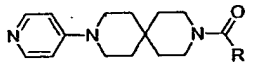
Table 1. In vitro activity for compounds with benzamidine group



Compds	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
1	$COCH_2CO_2H$	9.7	9.3
2	$CO(CH_2)_2CO_2H$	15	13.8
3	$CO(CH_2)_3CO_2H$	3.5	10.3
4	$CO(CH_2)_4CO_2H$	>100	18.8
5	$CH_2CH_2CO_2H$	0.16	1.15

[a]IC_{50} values expressed as the average of at least two determinations. The average error for the determinations was ±15%.

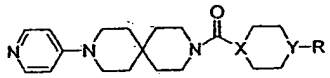
Table 2. In vitro activity for compounds with pyridines as the basic function



Compds	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
6	$(CH_2)_3CO_2H$	0.24	5.08
7	$(CH_2)_4CO_2H$	0.26	4.54
8	$(CH_2)_5CO_2H$	0.27	4.55
9	$(CH_2)_6CO_2H$	1.16	17.8

[a]See Table 1.

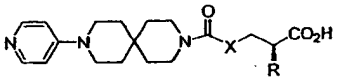
Table 3. Analogues with rigid carboxylic acid moiety



Compds	X	Y	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
15	N	CH	OCH_2CO_2H	0.21	2.65
16	CH	N	$COCH_2CO_2H$	0.043	1.17

[a]See Table 1.

Table 4. Modifications of the carboxylic acid function



Analogues	R	X	ELISA Fg/GPIIb-IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
10	NHCBz	CH_2	0.007	4.58
11	$NHCO_2n$But	CH_2	0.004	0.722
12	$NHSO_2n$But	CH_2	0.023	0.768
13	$NHSO_2$Tos	CH_2	0.002	0.078
14	$NHSO_2$isoxazole	CH_2	0.002	0.021
17	$NHSO_2$isoxazole	NH	0.001	0.039

[a]See Table 1.

this study were found to be highly selective towards GPIIb–IIIa.

The pharmacokinetic properties of analogue **14** (CT51688) as its free acid and as its ethyl ester prodrug were evaluated in Sprague–Dawley rats. The oral bioavailability of **14** was found to be 7.3% but was quite rapidly cleared. The oral bioavailability of the ethyl ester prodrug of **14** was even less (3.2%) than its free acid form. Although we were not successful in identifying oral GPIIb–IIIa antagonists with good pharmacokinetic properties, the 3,9-diazaspiro[5.5]undecane template has afforded potent and specific antagonists of GPIIb–IIIa. Further exploration of this template and other spirocyclic templates will be the subject of additional communications from our laboratories.

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